



Global Seabird Response to Forage Fish Depletion—One-Third for the Birds

Philippe M. Cury, *et al.*
Science **334**, 1703 (2011);
DOI: 10.1126/science.1212928

This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by [clicking here](#).

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines [here](#).

The following resources related to this article are available online at www.sciencemag.org (this information is current as of January 2, 2012):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/content/334/6063/1703.full.html>

Supporting Online Material can be found at:

<http://www.sciencemag.org/content/suppl/2011/12/21/334.6063.1703.DC1.html>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/content/334/6063/1703.full.html#related>

This article **cites 112 articles**, 23 of which can be accessed free:

<http://www.sciencemag.org/content/334/6063/1703.full.html#ref-list-1>

creasing demands of supporting and moving greater weight on land and the benefits of having more upright toe bones but directing some loads away from the toes with the predigits and fat pad, which resulted in the peculiar compromise that persists in the feet of extant elephants.

The recognition of elephant predigits as enlarged sesamoids that perform digit-like functions fuels inspiration for examining the evolution of foot function, terrestriality, and gigantism in other lineages. Sauropod dinosaurs had expansive foot pads, particularly in their pedes (24); however, no evidence of predigits has been found. Considering that the predigits form on the medial border of the feet, they would tend to be lost if digit I is lost or reduced, as it was in early perisodactyls and artiodactyls. This loss might limit foot pad expansion and thereby explain why rhinos and hippos seem to lack predigits [but see (18) for a possible rudimentary pollex in hippos] and have less expanded foot pads than elephants do (8). Regardless, the previously misunderstood and neglected predigits of elephants now deserve recognition as a remarkable case of evolutionary exaptation (4), revealing how elephants evolved their specialized foot form and function.

References and Notes

1. D. D. Davis, *Feldiana* 3, 1 (1964).
2. H. Endo *et al.*, *J. Anat.* **195**, 295 (1999).
3. S. J. Gould, *Nat. Hist.* **87**, 20 (1978).
4. S. J. Gould, E. S. Vrba, *Paleobiology* **8**, 4 (1982).
5. M. Fabrezi, *Zool. J. Linn. Soc.* **131**, 227 (2001).
6. M. R. Sánchez-Villagra, P. R. Menke, *Zoology* **108**, 3 (2005).
7. P. Blair, *Philos. Trans.* **27**, 53 (1710).
8. H. Neuville, *Arch. Mus. Natl. Hist. Nat. Paris* **13**, 6e Serie, 111 (1935).
9. K. von Bardeleben, *Proc. Zool. Soc.* **1894**, 354 (1894).
10. C. Mitgutsch *et al.* *Biol. Lett.*, 10.1098/rsbl.2011.0494 (2011).
11. Materials and methods are available as supporting material on Science Online.
12. G. E. Weisengruber *et al.*, *J. Anat.* **209**, 781 (2006).
13. F. Galis, J. J. M. van Alphen, J. A. J. Metz, *Trends Ecol. Evol.* **16**, 637 (2001).
14. J. Prochel, P. Vogel, M. R. Sánchez-Villagra, *J. Anat.* **205**, 99 (2004).
15. J. R. Hutchinson, C. E. Miller, G. Fritsch, T. Hildebrandt, in *Anatomical Imaging: Towards a New Morphology*, R. Frey, H. Endo, Eds. (Springer, Berlin, 2009), pp. 23–38.
16. C. E. Miller, C. Basu, G. Fritsch, T. Hildebrandt, J. R. Hutchinson, *J. R. Soc. Interface* **5**, 465 (2008).
17. D. R. Carrier, N. C. Heglund, K. D. Earls, *Science* **265**, 651 (1994).
18. A. B. Clifford, *J. Vertebr. Paleontol.* **30**, 1827 (2010).
19. N. Court, *Palaentogr. Abt. A* **226**, 125 (1993).
20. D. E. Lieberman *et al.*, *Nature* **463**, 531 (2010).
21. F. Michilsen, P. Aerts, R. Van Damme, K. D'Août, *J. Zool. (London)* **279**, 236 (2009).
22. A. A. Biewener, *Science* **250**, 1097 (1990).
23. M. N. Scholz, M. F. Bobbert, A. J. van Soest, J. R. Clark, J. van Heerden, *J. Exp. Biol.* **211**, 3266 (2008).
24. M. F. Bonnan, in *Thunder-Lizards: the Sauropodomorph Dinosaurs*, K. Carpenter, V. Tidwell, Eds. (Indiana Univ. Press, Bloomington, IN, 2005), pp. 346–380.
25. M. M. Smuts, A. J. Bezuidenhout, *Onderstepoort J. Vet. Res.* **69**, 1 (1993).

26. M. M. Smuts, A. J. Bezuidenhout, *Onderstepoort J. Vet. Res.* **61**, 51 (1994).
27. A. Boyde, R. Travers, F. H. Glorieux, S. J. Jones, *Calcif. Tissue Int.* **64**, 185 (1999).
28. C. Delmer, *Acta Palaeontol. Pol.* **54**, 561 (2009).
29. E. Gheerbrant, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 10717 (2009).
30. E. Gheerbrant, P. Tassy, *C. R. Palevol.* **8**, 281 (2009).

Acknowledgments: We thank the staff of the Structure and Motion Laboratory of the Royal Veterinary College for assistance and three anonymous reviewers for constructive criticism. Many individuals assisted with the collection of the cadaveric data; we particularly thank the European-based zoos that provided the specimens and G. Fritsch for CT scans done in Germany. O. Cosar, R. Weller, A. Wilson, and K. Jespers assisted with the ex vivo loading experiments. J. Molnar assisted with Figs. 1 to 4 and the movies. This project was funded by the Biotechnology and Biological Sciences Research Council (BBSRC) (grants BB/C51684/1 and BB/H002782/1 to J.R.H.). Additionally, A.A.P. appreciates funding from Arthritis Research UK and the BBSRC, and A.B. was supported by the Veterinary Advisory Committee of the UK Horserace Betting Levy Board. The data reported in this paper are tabulated in the SOM. The authors declare no conflicts of interest.

Supporting Online Material

www.sciencemag.org/cgi/content/full/334/6063/1699/DC1

Materials and Methods

SOM Text

Figs. S1 to S16

Tables S1 to S3

References (31–41)

Movies S1 to S4

20 July 2011; accepted 8 November 2011

10.1126/science.1211437

Global Seabird Response to Forage Fish Depletion—One-Third for the Birds

Philippe M. Cury,^{1*} Ian L. Boyd,^{2*} Sylvain Bonhommeau,³ Tycho Anker-Nilssen,⁴ Robert J. M. Crawford,⁵ Robert W. Furness,⁶ James A. Mills,⁷ Eugene J. Murphy,⁸ Henrik Österblom,⁹ Michelle Paleczny,¹⁰ John F. Piatt,¹¹ Jean-Paul Roux,^{12,13} Lynne Shannon,¹⁴ William J. Sydeman¹⁵

Determining the form of key predator-prey relationships is critical for understanding marine ecosystem dynamics. Using a comprehensive global database, we quantified the effect of fluctuations in food abundance on seabird breeding success. We identified a threshold in prey (fish and krill, termed “forage fish”) abundance below which seabirds experience consistently reduced and more variable productivity. This response was common to all seven ecosystems and 14 bird species examined within the Atlantic, Pacific, and Southern Oceans. The threshold approximated one-third of the maximum prey biomass observed in long-term studies. This provides an indicator of the minimal forage fish biomass needed to sustain seabird productivity over the long term.

Public and scientific appreciation for the role of top predators in marine ecosystems has grown considerably, yet many upper trophic level (UTL) species, including seabirds, marine mammals, and large predatory fish, remain depleted owing to human activities (1–4). Fisheries impacts include direct mortality of exploited species and the more subtle effects of altering trophic pathways and the functioning of marine ecosystems (5). Specifically, fisheries for lower trophic level (LTL) species, primarily small

coastal pelagic fish (e.g., anchovies and sardines), euphausiid crustaceans (krill), and squid (hereafter referred to as “forage fish”), threaten the future sustainability of UTL predators in marine ecosystems (6, 7). An increasing global demand for protein and marine oils contributes pressure to catch more LTL species (8). Thus, fisheries for LTL species are likely to increase even though the consequences of such activity remain largely unknown at the ecosystem level. It remains challenging, however, to assess fishing

impacts on food webs because numerical relationships between predators and prey are often unknown, even for commercially valuable fish (9, 10). Ecosystem models and ecosystem-based fisheries management, for which maintaining

¹Institut de Recherche pour le Développement, UMR EME-212, Centre de Recherche Halieutique Méditerranéenne et Tropicale, Avenue Jean Monnet, BP 171, 34203 Sète Cedex, France.

²Scottish Oceans Institute, University of St Andrews, St Andrews KY16 8LB, UK. ³Ifremer, UMR EME 212, Centre de Recherche Halieutique Méditerranéenne et Tropicale, Avenue Jean Monnet, BP 171, 34203 Sète Cedex, France. ⁴Norwegian Institute for Nature Research, Post Office Box 5685 Sluppen, NO-7485 Trondheim, Norway. ⁵Branch Oceans and Coasts, Department of Environmental Affairs, Private Bag X2, Rogge Bay 8012, South Africa. ⁶College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK. ⁷10527 A Skyline Drive, Corning, NY 14830, USA. ⁸British Antarctic Survey, High Cross, Madingley Road, Cambridge CB3 0ET, UK. ⁹Baltic Nest Institute, Stockholm Resilience Centre, Stockholm University, SE-106 91 Stockholm, Sweden. ¹⁰Fisheries Centre, Aquatic Ecosystems Research Laboratory (AERL), 2202 Main Mall, The University of British Columbia, Vancouver, BC, Canada V6T 1Z4. ¹¹U.S. Geological Survey, Alaska Science Center, 4210 University Drive, Anchorage, AK 99508, USA. ¹²Ecosystem Analysis Section, Ministry of Fisheries and Marine Resources, Lüderitz Marine Research, Post Office Box 394, Lüderitz, Namibia. ¹³Animal Demography Unit, Zoology Department, University of Cape Town, Private Bag X3, Rondebosch, Cape Town 7701, South Africa. ¹⁴Marine Research Institute and Zoology Department, University of Cape Town, Private Bag X3, Rondebosch, Cape Town 7701, South Africa. ¹⁵Farallon Institute for Advanced Ecosystem Research, Post Office Box 750756 Petaluma, CA 94952, USA.

*To whom correspondence should be addressed. E-mail: philippe.cury@ird.fr (P.M.C.); ilb@st-andrews.ac.uk (I.L.B.)

predator populations is an objective (2, 11, 12), will remain controversial until these relationships are more fully quantified.

To improve our understanding of the effects of LTL fisheries on marine ecosystems, more information on predator-prey relationships across a range of species and ecosystems is required (6). Seabirds are conspicuous members of marine ecosystems globally. Many aspects of seabird ecology have been measured consistently for decades, encompassing ecosystem change at multiple scales (13). Substantial long-term data sets on seabird breeding success have been compiled for many taxa in several marine ecosystems around the world (14–16), but for relatively few has independent information on prey availability been obtained concurrently. For those where prey data are available, temporal covariance in predators and their prey suggests that seabirds can be used as indicators of forage fish population fluctuations (7, 16, 17). Here, we used data collected contemporaneously over multiple decades from seabirds and forage fish to test the hypothesis that the form of the numerical response between seabird breeding success and forage fish abundance is consistent across species and ecosystems. We used data from seabird species that have strong dietary dependencies on forage fish prey and where the time series for both the predator and the prey have high spatial and temporal congruence. We compiled data from 19 time series covering seven marine ecosystems, nine sites, and 14 seabird species and their major prey (Fig. 1 and table S1). The data set included 438 data points spanning 15 to 47 colony-years per breeding site (table S1). The abundance of principal prey for each seabird species was estimated independently of the data collected from the birds, usually as part of population assessments conducted in support of fisheries management (table S1).

To examine empirical relationships between seabird breeding success and prey abundance, we used nonparametric statistical methods that facilitate nonlinear modeling by making no a priori assumptions about the form of the relationships (generalized additive models, or GAMs). Initially, each time series (seabird breeding success and prey abundance) was normalized by expressing the measurements as the number of standard deviations from the mean; this enables robust comparisons across species and ecosystems. Once the numerical relationship was established, we used a change-point analysis (sequential *t* tests that find the most likely point at which the slope of breeding success changes in relation to prey abundance) to identify thresholds within nonlinear relationships (18) (Fig. 2A). A bootstrap analysis was used to calculate confidence intervals of the threshold, and the variance in seabird breeding success was calculated for each prey abundance class. Last, a selection of a priori parametric models ranging from linear, sigmoid, asymptotic, to hierarchical (table S2) was fitted to the general relationship. The most parsimonious

model was then used to fit the relationship between seabird breeding success and forage fish population size for each ecosystem (pooling all species) and each seabird species (pooling all ecosystems).

Seabird breeding success showed a nonlinear response to changes in prey abundance (Fig. 2A). The threshold at which breeding success began to decline from the asymptote was not significantly different from the long-term mean of prey abundance (range -0.30 and $+0.13$, standard deviation of the mean, Fig. 2A). The threshold was 34.6% (95% confidence interval 31 to 39%), or approximately one-third of the maximum observed prey abundance. The coefficient of variation between the different thresholds among species and ecosystems was 28% (table S1). All time series were of sufficient duration to identify the threshold (detection is possible after 13 years of observation, fig. S1) and the maximum biomass (detection is possible after 11 years, fig. S2). Variance in breeding success increased significantly (*F* test, $P < 10^{-4}$) below the threshold of prey abundance (Fig. 2B). Fitting parametric models to individual responses showed a similar inflection point and similar asymptotic values across ecosystems and species (Figs. 2, C and D, and 3), indicating that the functional form was a general feature of the seabird–forage fish relationship.

The asymptotic form of the relationship between seabird breeding success and forage

fish abundance has been reported previously (15, 16, 19–24), but the common scaling across species and ecosystems and the consistency of threshold values are new observations. The global pattern shows a threshold below which the numerical response declines strongly as food abundance decreases and above which it reaches a plateau and does not change even as food abundance increases. This pattern is apparently robust to the varying life-history strategies, habitat preferences, and population sizes of the seabird species considered. Nonetheless, we acknowledge that a range of factors may interact to weaken or possibly accentuate the relationship between seabird breeding performance and prey species abundance. Alternative drivers of change in breeding success include changes in habitat characteristics or predation pressures, or complex intercolony dynamics. Predators may also show more or less capacity to switch to alternative prey items, which may buffer productivity against declines in any single prey species (25).

Periods of consistently high or low breeding success, or occasional complete breeding failures, are normal in seabirds, and most species are adapted to fleeting anomalous environmental conditions. However, chronic food scarcity, as potentially defined by prey abundance below the threshold described here for seabirds, will compromise long-term breeding success, and this may affect the trajectory of their populations.

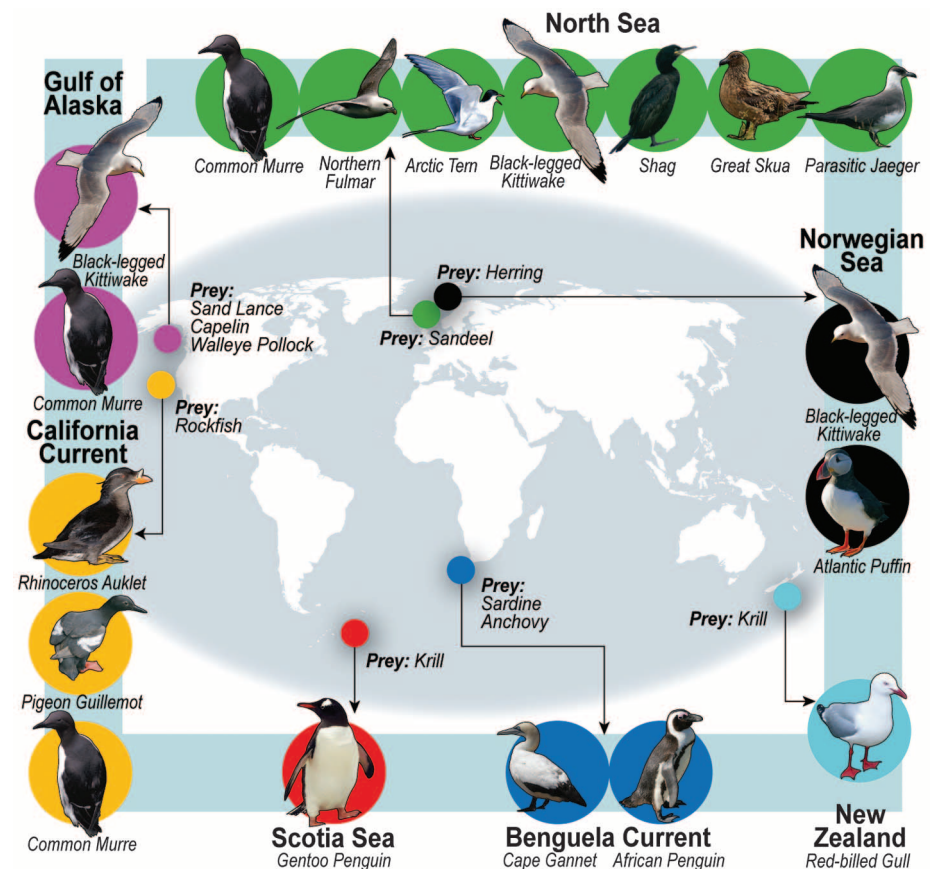


Fig. 1. Map of the distribution of seabird and prey species considered in our analysis.

Fig. 2. (A) Relationship between normalized annual breeding success of seabirds and normalized prey abundance. Each data point from all the time series was plotted with the predictions of a generalized additive model (GAM) (solid line). The gray area represents the 95% confidence interval of the fitted GAM. The threshold in the nonlinear relationship (black solid vertical line) and its 95% confidence interval (black dashed vertical lines) were detected from a change-point analysis. (B) Change in variance across the range of normalized food abundance ranging from -1.5 to 2 standard deviations in eight classes. Variance below the threshold was 1.8 times higher than above it. (C and D) Similar relationships were present when data were pooled (C) for species within ecosystems and (D) for species pooled among ecosystems using the best-fitting asymptotic model (table S2). The Arctic Tern (not shown) model fit was not significant (table S1). The colors in (A) and (C) represent the data set for each ecosystem and in (D) for each seabird species.

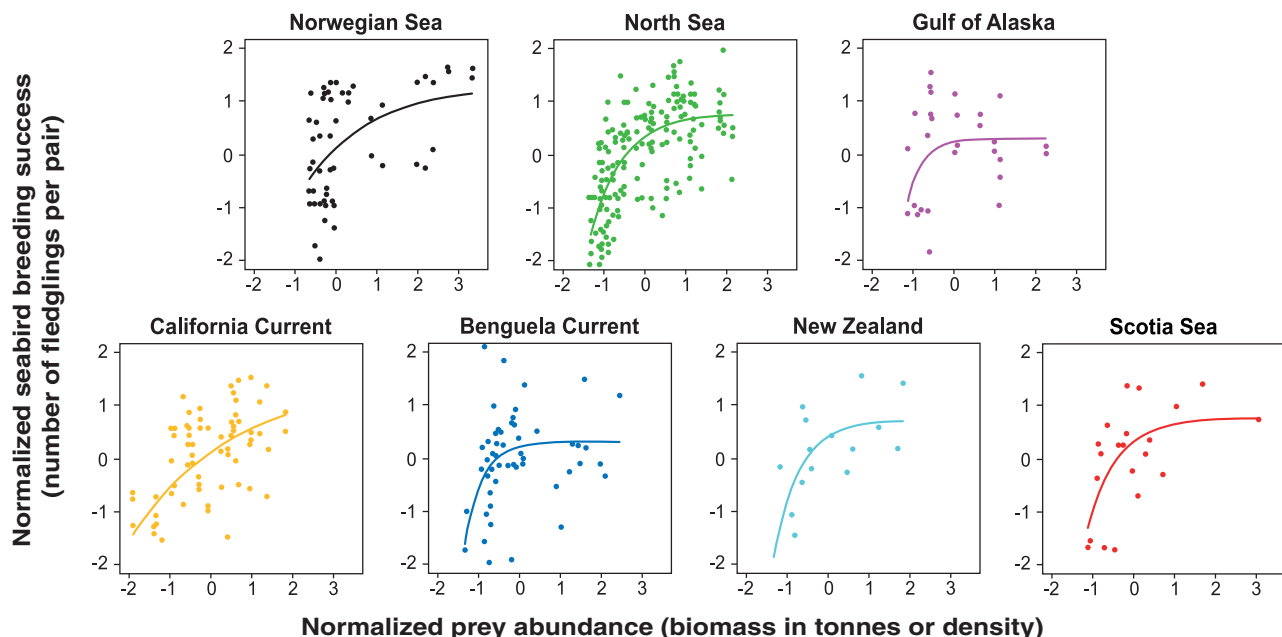
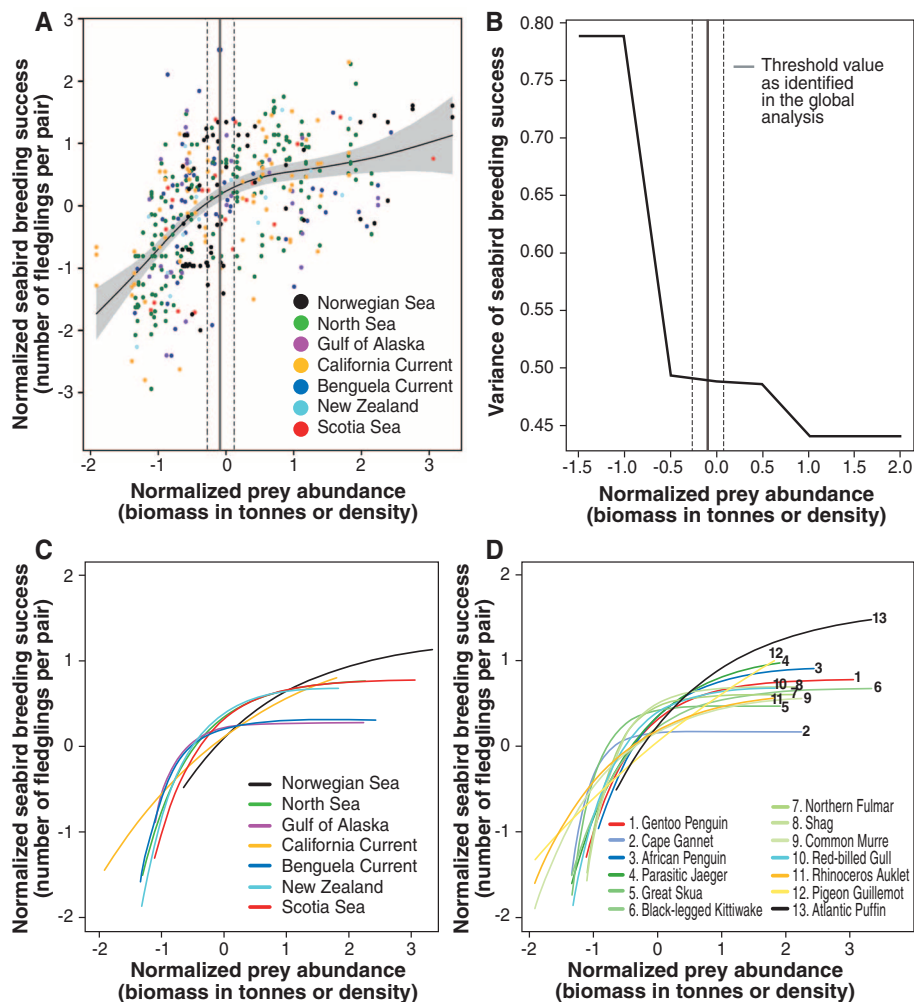


Fig. 3. Relationship between normalized annual breeding success of pooled seabird species and normalized prey abundance for the seven different ecosystems using the most parsimonious asymptotic model (table S2).

Indeed, food scarcity can also reduce adult survival in seabirds (26), with immediate population-level impacts. Whether caused by persistent overfishing, or directional or stochastic environmental change that reduces ecosystem carrying capacity, recruitment and survival will probably have thresholds of prey abundance shifted to the left of that for breeding success (15, 16). Consequently, the threshold for breeding success is likely to provide a precautionary guideline to what level of food reduction might seriously impact seabird populations.

The threshold defined by our study suggests that if management objectives include balancing predator-prey interactions to sustain healthy UTL predator populations and ecosystem functions (2), a practical indicator would be to maintain forage fish biomass above one-third of the maximum observed long-term biomass. The application of such a management guideline will depend upon local circumstances, such as the need to implement spatial management around breeding colonies or the conservation status of species (27). Although we cannot assume similarity between all taxa in the value of the predator-prey threshold, our study demonstrates consistency among a broad range of seabirds. There is also evidence that some marine mammals and predatory fish share the general form of the relationship (17, 19, 25, 28).

Tuning management goals to ensure sufficient biomass of forage fish for seabird reproduction may be a useful step toward ensuring sustainability of predator-prey interactions for other, less well-studied predators in marine ecosystems. Even for predators not showing high dependency on exploited species, this is likely to provide a precautionary step. The “one-third for the birds” guiding principle could be applied widely to help

manage forage fisheries to benefit ecosystem resilience. Indeed, predator responses of this type are already included in some specific management systems (29). Although such a guideline might be difficult to consider for new fisheries, where there are few data to determine the maximum biomass, most of the economically important coastal pelagic fish populations have sufficient data to define the threshold in many ecosystems (e.g., in the Benguela, California, and Humboldt Currents) (figs. S1 and S2).

The generality of the asymptotic form of the predator-prey relationship suggests that it is rooted in fundamental life history and ecological theory (e.g., demographic trade-offs and functional responses). In a practical context, “one-third for the birds” is a simple, empirically derived guiding principle that embraces the ecosystem approach to management aimed at sustaining the integrity of predator-prey interactions and marine food webs for the benefit of both natural predators and humans.

References and Notes

1. J. B. C. Jackson *et al.*, *Science* **293**, 629 (2001).
2. E. K. Pikitch *et al.*, *Science* **305**, 346 (2004).
3. H. K. Lotze, B. Worm, *Trends Ecol. Evol.* **24**, 254 (2009).
4. M. Hoffmann *et al.*, *Science* **330**, 1503 (2010).
5. M. Coll, S. Libralato, S. Tudela, I. Palomera, F. Pranovi, *PLoS ONE* **3**, e3881 (2008).
6. A. D. M. Smith *et al.*, *Science* **333**, 1147 (2011).
7. P. Cury *et al.*, *ICES J. Mar. Sci.* **57**, 603 (2000).
8. R. L. Naylor *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 15103 (2009).
9. P. A. Abrams, L. R. Ginzburg, *Trends Ecol. Evol.* **15**, 337 (2000).
10. I. C. Stige *et al.*, *Proc. R. Soc. Lond.* **277**, 3411 (2010).
11. H. M. Pereira *et al.*, *Science* **330**, 1496 (2010).
12. T. P. Dawson, S. T. Jackson, J. I. House, I. C. Prentice, G. M. Mace, *Science* **332**, 53 (2011).

13. R. D. Wooller, J. S. Bradley, J. P. Croxall, *Trends Ecol. Evol.* **7**, 111 (1992).
14. R. W. Furness, K. Camphuysen, *ICES J. Mar. Sci.* **54**, 726 (1997).
15. D. K. Cairns, *Biol. Oceanogr.* **5**, 261 (1987).
16. J. F. Piatt *et al.*, *Mar. Ecol. Prog. Ser.* **352**, 221 (2007).
17. I. L. Boyd, *Aquat. Conserv.* **12**, 119 (2002).
18. T. Andersen, J. Carstensen, E. Hernández-García, C. M. Duarte, *Trends Ecol. Evol.* **24**, 49 (2009).
19. I. L. Boyd, A. W. A. Murray, *J. Anim. Ecol.* **70**, 747 (2001).
20. J. M. Durant, T. Anker-Nilssen, N. C. Stenseth, *Proc. Biol. Sci.* **270**, 1461 (2003).
21. K. Reid, J. Croxall, D. Briggs, E. Murphy, *ICES J. Mar. Sci.* **62**, 366 (2005).
22. R. W. Furness, *J. Ornithol.* **148** (suppl. 2), 247 (2007).
23. J. A. Mills *et al.*, *J. Anim. Ecol.* **77**, 1129 (2008).
24. J. C. Field, A. D. MacCall, R. W. Bradley, W. J. Sydeman, *Ecol. Appl.* **20**, 2223 (2010).
25. M. E. Hunsicker *et al.*, *Ecol. Lett.* **14**, 1288 (2011).
26. A. S. Kitaysky *et al.*, *Funct. Ecol.* **24**, 625 (2010).
27. L. Pichegru, D. Grémillet, R. J. Crawford, P. G. Ryan, *Biol. Lett.* **6**, 498 (2010).
28. J. F. Piatt, D. A. Methven, *Mar. Ecol. Prog. Ser.* **84**, 205 (1992).
29. D. J. Agnew, *Antarct. Sci.* **9**, 235 (1997).

Acknowledgments: This work was partly funded by Eur-Oceans Consortium, the Institut de Recherche pour le Développement (IRD), the Lenfest Forage Fish Task Force, Mistra, the Sea Around Us Project, and the South African Research Chair Initiative. Disclaimers and acknowledgment of institutes and collaborators are provided in the SOM. Data, methods, and codes are available in the SOM.

Supporting Online Material

www.sciencemag.org/cgi/content/full/334/6063/1703/DC1
Materials and Methods
Figs. S1 to S4
Tables S1 and S2
References (30–138)
Data and Codes

19 August 2011; accepted 8 November 2011
10.1126/science.1212928

Mouse B-Type Lamins Are Required for Proper Organogenesis But Not by Embryonic Stem Cells

Youngjo Kim,^{1,2} Alexei A. Sharov,³ Katie McDole,^{1,2,4} Melody Cheng,⁵ Haiping Hao,⁶ Chen-Ming Fan,^{1,4} Nicholas Gaiano,⁵ Minoru S. H. Ko,^{3*} Yixian Zheng^{1,2,4*}

B-type lamins, the major components of the nuclear lamina, are believed to be essential for cell proliferation and survival. We found that mouse embryonic stem cells (ESCs) do not need any lamins for self-renewal and pluripotency. Although genome-wide lamin-B binding profiles correlate with reduced gene expression, such binding is not directly required for gene silencing in ESCs or trophoblast cells. However, B-type lamins are required for proper organogenesis. Defects in spindle orientation in neural progenitor cells and migration of neurons probably cause brain disorganizations found in lamin-B null mice. Thus, our studies not only disprove several prevailing views of lamin-Bs but also establish a foundation for redefining the function of the nuclear lamina in the context of tissue building and homeostasis.

The major structural components of the nuclear lamina found underneath the inner nuclear membrane in metazoan nuclei are type V intermediate filament proteins called

lamins (1). Mammals express both A- and B-type lamins encoded by three genes, *Lmna*, *Lmnb1*, and *Lmnb2*. *Lmnb1* and *Lmnb2* express lamin-B1 and -B2, respectively. *Lmnb2* also expresses

lamin-B3 through alternative splicing in testes. Mutations in lamins have been linked to a number of human diseases referred to as laminopathies (2), although the disease mechanism remains unclear. A-type lamins are expressed only in a subset of differentiated cells and are not essential for basic cell functions (3, 4). By contrast, at least one B-type lamin is found in any given cell type. Because numerous functions, including transcriptional regulation, DNA replication, and regulation of mitotic spindles, have been assigned to B-type lamins, they are thought to be essential for basic cell proliferation and survival (1, 5–8).

¹Department of Embryology, Carnegie Institution for Science, Baltimore, MD 21218, USA. ²Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA. ³Developmental Genomics and Aging Section, Laboratory of Genetics, National Institute on Aging, NIH, Baltimore, MD 21224, USA. ⁴Department of Biology, Johns Hopkins University, Baltimore, MD 21218, USA. ⁵Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. ⁶Microarray Core Facility, Johns Hopkins University School of Medicine, Baltimore, MD 21209, USA.

*To whom correspondence should be addressed. E-mail: zheng@ciwemb.edu (Y.Z.), kom@grc.nia.nih.gov (M.S.H.K.)